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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/498,098 | 02/04/2000 | Jeffrey Stack | AURO1330 | 8316 |

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| EXAMINER | |
|---|---|
| ANGELL, JON E | |
| **ART UNIT** | **PAPER NUMBER** |
| 1635 | |

DATE MAILED: 03/07/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/498,098 | STACK ET AL. | |
| | Examiner | Art Unit | |
| | Jon Eric Angell | 1635 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *02 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-6,9,11-31,34-38,50,55,60 and 83-86* is/are pending in the application.

4a) Of the above claim(s) *55* is/are withdrawn from consideration.

5)☒ Claim(s) *50 and 60* is/are allowed.

6)☒ Claim(s) *1-6,9,11-15,17-31,34-38,85 and 86* is/are rejected.

7)☒ Claim(s) *16,83 and 84* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

The amendment filed 12/2/05 is acknowledged. The amendment has been entered. Claims 1-6, 9, 11-31, 34-38, 50, 55, 60 and 83-86 are currently pending in the application and are addressed herein.

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Claim 55 has been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/2/2001.

Claims 1-6, 9, 11-31, 34-38, 50, 60 and 83-86are examined herein.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 9, 11-15, 17-22, 38 and 83-86 are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the entire scope of the claims. The specification does not enable any person skilled in the art to which it pertains,

or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

There are two specific issues that render the instant claims not fully enabled. First, Claims 1 and 23 are drawn to a method comprising providing a cell at least one destabilization domain, a reporter moiety/target protein, and a linker moiety that operatively couples the destabilization domain(s) and the reporter moiety/target protein wherein the linker moiety comprises a protease cleavage site and cleavage of said linker moiety by said protease decreases the coupling of the destabilization domain(s) thereby increasing the stability of the reporter moiety/target protein wherein the destabilization domain(s), reporter moiety/target protein and linker domain are encoded by one or more nucleic acid molecules in the cell. Based on the disclosure of the specification, one of skill in the art would only envisage the instant claims (claims 1 and 23 as well as their dependent claims) as being drawn to a single polypeptide comprising the three specific domains: the destabilization domain(s), the reporter moiety/target protein, and the linker domain which comprises a protease cleavage site. Considering that the linker domain comprises a protease cleavage site when cleaved by a protease decreases the coupling of the destabilization domain(s) and the reporter/target protein the only reasonable use for these domains together is for either (1) detecting a protease activity, or (2) increasing the concentration of the target protein. Since the specification only appears to disclose the linker domain comprising a protease cleavage as part of a single polypeptide wherein the polypeptide comprises destabilization domain(s), the linker domain, and a reporter/target protein, and considering one of skill in the art would not reasonably envisage the three domains to work together as set forth in the claims when the three domains are not expressed as a single

polypeptide, the specification has not provided an enabling disclosure for the entire scope encompassed by the instant claims. Specifically, the specification does not provide an enabling disclosure for the instant claims wherein the three domains are encoded by more than one nucleic acid molecule. Therefore, limiting claims 1 and 23 to "a polynucleotide molecule" would obviate this rejection. It is acknowledged that the instant specification contemplates using the disclosed system to identify protein-protein interactions and also contemplates the linker can comprise protein interaction domains (such as SH1 or SH2 domains) such that the domains can be encoded by more than one polynucleotide sequences. However, the instant claims are specifically limited to the linker domain comprising a protease cleavage site such that the system can is useful for assaying protease activity or for increasing the concentration of the reporter/target protein. The only way one of skill in the art would understand the instant protease cleavage linker domain system to work would be when the system is expressed as a single polypeptide comprising the destabilization domain, linker and reporter/target protein.

Furthermore, claims 1 and 38 are drawn to methods of using a cell wherein the cell is specifically indicated to be in vitro. However, claims 85 and 86 specifically indicate that the cells are from a transgenic rodent and plant, respectively. Furthermore, claims 83 and 84 indicate that the cells are from an organism other than a transgenic organism. Since claims 83 and 84 must, be definition further limit claims 1 and 38, claims 1 and 38 must encompass a method of using a cell in vitro wherein the cell is from either a transgenic or non-transgenic organism. Furthermore, claim 1 clearly must encompass transgenic organism because claims 85 and 86 explicitly indicate that the cells are from transgenic organisms. Considering that the claims encompass using a cell of a transgenic organism, in order for claims 1 and 38 (as well as

their dependent claims) to be fully enabled the specification must provide an enabling disclosure for making the transgenic organisms encompassed by the claims. However, the specification does not provide an enabling disclosure for making the transgenic organisms that have been genetically engineered to express the destabilization domain-linker-reporter/target protein. It is noted that canceling claims 83-86 would obviate this rejection.

The specification discloses how a cell can be engineered to express the chimeric destabilized polypeptide in vitro by transducing a nucleic acid encoding the chimeric polypeptide into a cell in vitro (see Example 8, page 74 of the specification). Furthermore, the specification contemplates transgenic animals comprising a nucleic acid sequence encoding the chimeric polypeptide and methods of making and using the transgenic animals (see p. 8 of the specification; as well as pages 59-62). Therefore, claims 1 and 38 clearly encompass methods of using cells from transgenic organisms. As such, the claims are very broad and embrace transgenic organisms (including animals, plants and insects) engineered to express the chimeric destabilized polypeptide.

There is no evidence presented in the specification that any transgenic multicellular organisms that express the chimeric polypeptide have been successfully produced.

The state of the art at the time of filing regarding the production of transgenic organisms was and continues to be unpredictable. For instance, it is well known in the art that the level and the specificity of expression of a transgene, as well as the phenotype are greatly dependent on the specific transgene construct used. The individual gene of interest, promoter, enhancer, coding, or non-coding sequences present in the transgene construct, the site of integration, etc. are all important factors in controlling the expression of the transgene. The art also recognizes

problems with regard to producing animals of different species with identical phenotypes even when using a particular transgene to create both transgenic animals. For example, Wall (Theriogenology, Vol. 45, pages 57-68, 1996; previously cited) teaches the unpredictability of transgene behavior due to factors such as position effect and unidentified control elements resulting in a lack of transgene expression or variable expression (paragraph bridging pages 61-62). Furthermore, Overbeek (Transgenic Animal Technology, pages 96-98, 1994; previously cited) teaches that there can be considerable variation in the level of transgene expression in different transgenic animals (page 96, last paragraph). Therefore, the prior art recognized that creating transgenic organisms having a particular desired phenotype is unpredictable. In the instant case, the particular desired phenotype is the expression of the chimeric polypeptide at level sufficient to perform the claimed methods.

In addition, the species-specific requirements for transgene design are not clearly understood. Examples in the literature aptly demonstrate that even closely related species carrying the same transgene construct can exhibit widely varying phenotypes. For example, several animal models of human diseases have relied on transgenic rats when the development of mouse models was not feasible. Mullins et al. (1990; previously cited) produced outbred Sprague-Dawley x WKY rats with hypertension caused by expression of a mouse *Ren-2* renin transgene. Hammer et al. (1990 previously cited) describe spontaneous inflammatory disease in inbred Fischer and Lewis rats expressing human class I major histocompatibility allele HLA-B27 and human $\beta_2$-microglobulin transgenes. Both investigations were preceded by the failure to develop similar phenotypes in transgenic mice expressing the same transgenes that successfully caused the desired symptoms in transgenic rats (see Mullins et al., 1989; and Taurog et al., 1988,

both previously cited). Therefore, one of skill in the art cannot readily predict that any transgenic organism will have the desired phenotype of interest without actually creating the transgenic organism.

The specification only discloses general methods for producing transgenic animals and transgenic plants (see pages 59-67). The specification does not disclose working examples or provide guidance which would overcome the art-recognized problems indicated above. Therefore, one of skill in the art could not predictably and reliably make the transgenic plants, animals or insects encompassed the claims without performing an undue amount of additional experimentation.

Therefore, in view of the breadth of the claims, the limited amount of direction and/or guidance provided in the specification, the art recognized unpredictability with respect to making the transgenic organisms whose cells are encompassed by the claims and the limited working examples, it is concluded that an undue amount of experimentation is required for one skilled in the art to make and use the claimed invention to the full scope encompassed by the claims.

### *Allowable Subject Matter*

Claims 50 and 60 are allowed.

Claims 16, 83 and 84 are objected to because they depend on a rejected claim.

### *Response to Arguments*

With respect to the rejection of claims under 35 USC 112, 1st paragraph (scope of enablement) applicants argue that they have limited claims to in vitro methods which should

obviate the rejection. In response, it is acknowledged that the independent claims have been amended to indicate the methods are performed in vitro. However, as indicated above, claims 83-86 explicitly indicate that the cells are either from non-transgenic or transgenic organisms. As such, although the instant claims are limited to in vitro methods, the claims still encompass using cells isolated from transgenic organisms in the in vitro methods. The specification does not provide an enabling disclosure for how to make the transgenic organism encompassed by the claims for the reasons indicated above. Therefore, Applicants arguments are not persuasive as they pertain to the instant rejection of the indicated claims.

With respect to the rejection of claims under 35 USC 112, 1st paragraph (written description and enablement) the amendment to the claims has rendered to the rejection moot.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

J.E. Angell, Ph.D.
Art unit 1635

JON ANGELL
PATENT EXAMINER